

Submitted by:

Emanuela Saracco, Pharm.D.

Global Medical Information, Medical Affairs.

AbbVie Inc.

ABV1-2NW10203

1 North Waukegan Rd

North Chicago, IL 60064

Phone: 847-938-8174

Email: emanuela.saracco@abbvie.com

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NCCN Guidelines® Panel: Acute Myeloid Leukemia

On behalf of AbbVie and Genentech, I respectfully request the NCCN Acute Myeloid Leukemia (AML) Guidelines Panel to consider the enclosed, recently published data for Venclexta® (venetoclax) in combination with azacitidine (AZA) in newly diagnosed AML patients ineligible for intensive chemotherapy (IC). This submission contains the full manuscript with safety and efficacy data of venetoclax in combination with AZA from the VIALE-A trial recently published in the New England Journal of Medicine (NEJM) to be considered along with the recent submission (sent July 12, 2020) to the panel.

Specific changes recommended within the NCCN Guidelines

- Consider inclusion of venetoclax + HMAs (AZA or DEC) as a category 1 preferred regimen for patients with newly diagnosed AML ≥60 years of age with and without actionable mutations who are not candidates for intensive remission induction therapy or decliners (AML-6).

FDA Clearance:

Venclexta® (venetoclax) is a BCL-2 inhibitor indicated in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly-diagnosed acute AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.¹ This indication is approved under accelerated approval based on response rates. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rationale:

The results of a phase 3, double-blind, placebo controlled, randomized trial (VIALE-A) in treatment-naïve AML patients were recently published in the NEJM.² The primary endpoint of the study was overall survival (OS). Key secondary endpoints included rates of complete remission (CR), CR + CR with incomplete count recovery (CR/CRi), CR/CRi by initiation of cycle 2, CR + CR with incomplete hematologic recovery (CR/CRh), transfusion independence (TI), outcomes by molecular subgroups (including IDH1/2 and FLT3), and safety. Clinically meaningful and statistically significant improvement in OS and remission rates were observed in patients who received treatment with Ven + AZA compared to AZA alone.

As of the data cut-off date of January 4, 2020, 286 patients were randomized to receive 400 mg Ven in combination with AZA and 145 patients were randomized to receive AZA + PBO. Median duration of follow-up was 20.5 months (range, <0.1 – 30.7). The median OS was 14.7 months in Ven + AZA and 9.6 months in AZA + PBO (HR: 0.66, 95% CI: 0.52–0.85, $P < 0.001$) respectively, representing a 34% reduction in risk of death.

Treatment with Ven + AZA led to a significant improvement in CR/CRi (66.4% vs 28.3%, $P < 0.001$ in the Ven + AZA and AZA + PBO arms, respectively). The median time to first CR/CRi was 1.3 months (range, 0.6 – 9.9) and 2.8 months (range, 0.8 – 13.2), respectively. By start of cycle 2, CR/CRi was achieved in 43.4% of Ven + AZA patients and in 7.6% of PBO + AZA patients. The median duration of CR/CRi was 17.5 months (95% CI, 13.6 to not reached [NR]) in the Ven+AZA arm and 13.4 months (95% CI, 5.8 to 15.5) in the AZA + PBO arm. Similarly, a statistically significant and clinically meaningful increase in CR/CRh was achieved in 64.7% of Ven + AZA treated patients compared to 22.8%, $P < 0.001$ in PBO + AZA treated patients. The median time to first CR/CRh was 1.0 month (range, 0.6 to 14.3) and 2.6 months (range, 0.8 to 13.2). Complete remission rates observed for patients treated with Ven + AZA vs AZA + PBO were 36.7% and 17.9%, respectively.

At baseline, genetic mutations of IDH1/2 and FLT3 were observed in the Ven + AZA (25% and 14%) and AZA + PBO (22% and 20%) arms. Overall survival was significantly higher in the Ven + AZA arm compared with the AZA + PBO arm in patients with IDH1/2 (HR 0.3, 95% CI 0.2-0.6) and was favored in patients with FLT3 (HR 0.66, 95% CI 0.35-0.1.26) mutation. In addition, a statistically significant improvement in CR/CRi was observed in patients with IDH1/2 mutations treated in the Ven + AZA group (75.4% [95% CI, 62.7 to 85.5]) vs the AZA + PBO group (10.7% [95% CI, 2.3 to 28.2]), respectively ($P < 0.001$); in those with FLT3 mutations, the CR/CRi was 72.4% (95% CI, 52.8 to 87.3) and 36.4% (95% CI, 17.2 to 59.3), respectively ($P = 0.02$).

A total of 427 patients were included in the safety analysis (Ven + AZA, N = 283; PBO + AZA, N = 144). Patients in the VEN + AZA arm received a median of 7.0 (range: 1.0–30.0) treatment cycles compared to 4.5 (range: 1.0–26.0) cycles on the AZA + PBO arm. The most common non-hematologic AEs of any grade ($\geq 20\%$ of patients) in the VEN + AZA vs AZA + PBO arms were nausea (44% vs 35%), constipation (43% vs 39%), diarrhea (41% vs 33%), vomiting (30% vs 23%), hypokalemia (29% for both), peripheral edema (24% vs 18%), pyrexia (23% vs 22%), decreased appetite (25% vs 17%), fatigue (21% vs 17%), and pneumonia (23% vs 27%). The most common Grade 3/4 AEs were hematologic in nature and included thrombocytopenia (45% vs 38%), neutropenia (42% vs 29%), febrile neutropenia (42% vs 19%), anemia (26% vs 20%), and leukopenia (21% vs 12%) in the Ven + AZA vs AZA + PBO arms, respectively. Tumor lysis syndrome was reported during ramp-up in 3 (1%) patients in the Ven + AZA arm and none in the AZA + PBO arm; all were transient biochemical changes that resolved with uricosuric agents and calcium supplements without treatment interruption.

The following cited prescribing information and published article is submitted in support of this proposed amendment:

1. Venclexta® [package insert]. Chicago, IL: AbbVie, Inc., 2019.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.

Respectfully submitted,



Emanuela Saracco, Pharm.D.
Manager, Global Medical Information, AbbVie Inc.